Global Regulatory Policy

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Food and Drug Administration
5630 Fishers Lane, Rm. 1061
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RE: [Docket No. 2004D-0188] – Draft Guidance for Industry on Development and Use of Risk Minimization Action Plans - Request for Comments

Merck & Co., Inc. is a leading worldwide, human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many important pharmaceutical products available today. These products have saved the lives of or improved the quality of life for millions of people globally.

Merck supports regulatory oversight of pharmaceutical product development and welcomes guidance for compliance that is based on sound scientific principles and good judgment. As a leading pharmaceutical company, Merck has extensive experience in thoroughly evaluating our products from discovery to approval and throughout their marketing life to assure that they continue to provide health benefits with minimum risk. Therefore, we are well qualified to comment on the risk assessment and risk management draft guidance documents issued by FDA on May 5, 2004[1]. Herein, we are providing comment on the draft guidance for industry entitled: *Development and Use of Risk Minimization Action Plans.*

General Comments

We commend the FDA for its efforts in the development of guidance for industry on good practices for risk assessment, risk management, and pharmacovigilance, and particularly for its prior issuance[2] of the three concept papers to encourage discussion of these important topics. The practice of issuing concept papers describing novel regulatory approaches, prior to issuance of draft guidance documents is fully supported by Merck.

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[1] 69 FR 25130, Docket No. 2004D-0188
[2] 68 FR 11120, Docket No. 02N-0528

The concept paper provides one additional opportunity for interested parties to provide comment and is a valuable tool when guidance documents describing new regulatory concepts are developed. We fully recognize the extra efforts that the concept paper precipitates and we appreciate the agency's continued commitment to this approach.

Risk assessment and risk management must be considered as part of a continuum from discovery through the marketing life of a product. As such, we are requesting that throughout the guidance document, the life-cycle approach to risk management be stressed. It will be imperative to recognize that risk minimization action plans (RiskMAPs) are not static documents but should be updated as new information warrants. The periodic reassessment of the risk management plan may result in a revision of the plan to increase the level of assessment, decrease the level or support elimination of the risk management plan altogether.

We commend the FDA for recognizing that the role of risk management planning is not to create a complex RiskMAP for every product (Lines 68-77: "*Many recommendations in this guidance are **not** intended to be generally applicable to all products...As a result, many of the recommendations presented here focus on situations when a product may pose an unusual type or level of risk.*") For most products, appropriate product labeling along with good post-marketing surveillance is sufficient. We encourage the Agency to continue to emphasize this important concept both internally and in public comment. It will be important to define the "*unusual type or level of risk*" that may warrant a RiskMAP, as this may be over (or under) interpreted by individuals. We recognize that it is not appropriate to define a listing of unusual risks, and that each developmental program must be looked at in toto, on a case-by-case basis.

Given the implications of a RiskMAP on the potential viability of a product and the resource requirements for such programs, we recommend that FDA promulgate a reviewer guidance or MAPP providing general guidelines to promote consistency across Centers, Divisions and review teams for proposing a that a RiskMAP be developed for a particular product and to create a level playing field for sponsors.

While the draft guidance notes that "*To the extent possible, this guidance conforms with FDA's commitment to harmonize international definitions and standards as applicable*" (Line 88 – 89) we stress that harmonization with international guidance, such as ICH E2E, is critical. RiskMAPs are linked to the product and should not be subjected to region-specific vagaries. The objectives of ICH have been to identify and correct unnecessary redundancies and time-consuming inefficiencies in development of pharmaceutical products caused by incompatible regulatory schemes. Global harmonization of principles of effective RiskMAPs is important to assure effective resource utilization in the generation of the information necessary to optimize benefit-risk balance. We support that the format/content of RiskMAPs should be driven by ICH E2E, with MEDRA accepted as the dictionary of choice.

Conclusion

We commend the Food and Drug Administration for issuance of the three concept papers, followed by draft guidance documents, on premarketing risk assessment, risk minimization action plans, and good pharmacovigilance practices and pharmacoepidemiologic assessment. These documents, along with the public workshop on April 9, 10, and 11, 2003 represent an extraordinary effort on the part of the Agency to convey its preliminary thoughts on these issues and to stimulate discussion with stakeholders.

The call for guidance on risk assessment, risk management, and pharmacovigilance activities in the PDUFA III goals is neither an expression of concern that current efforts are inadequate nor a call for more intense surveillance. It simply a call to document those practices that represent the best of what we are doing now. Risk management, itself, is not new to drug development. As an industry, in conjunction with the FDA, we have been conducting pre-approval tests of increasing intensity and complexity on potential products for decades; we have been collecting, monitoring, and evaluating spontaneous reports on marketed products and taking appropriate action to minimize risks. Likewise, we have carried out Phase 4 programs based on commitments made to the Agency at the time of approval to address potential, often theoretical, risks that had not been resolved at the time of approval. It is the best of these practices that the guidance is intended to capture, along with fostering international harmonization with the approach.

We appreciate the opportunity to share our comments with respect to FDA's Draft Guidance for Industry: Development and Use of Risk Minimization Action Plans. Please do not hesitate to contact me, should you have any questions.

Sincerely,

Lauren M. Hetrick

for Donald M. Black, MD, MBA
Vice President
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